MIDBRAIN RETICULAR STIMULATION AND GENERALIZED DRIVE

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INTRODUCTION

The idea that reticular activation and generalized drive might be functionally related has been stated by Berlyn (1960), Dell (1958), Hebb (1955), Lindsley (1951, 1958, 1961), Malmo (1959), Morgan (1957), and Schlosberg (1954). For example, Hebb (1955, p. 249) has stated that ". . . arousal . . . is synonomous with a general drive state . . .," and Dell (1958, p. 196) has remarked that "It [the reticular formation] provides the active source of continued excitation referred to by psychologists as 'motive', 'sensitizing component', 'drive', etc."

On the basis of psychological data, Brown (1953, 1961) has argued convincingly for the concept of drive that includes an intensity dimension but no directive function. A similar view has been expressed by Duffy (1951, 1957). According to the theoretical formulations of Hull (1943) and Spence (1956), an increase in nonspecific drive level will heighten the vigor and/or efficiency of ongoing behavior, regardless of the particular source of the drive. Thus, if the reticular formation (RF) serves as a central mechanism for generalized drive, direct stimulation of this region should produce performance effects identical to those brought about by manipulation of

motivational variables. That is, a wide variety of behaviors should be affected by reticular stimulation regardless of the source of drive employed during training, and the nature of the performance change should parallel that produced by an increase in drive from any other source.

There is a great deal of indirect evidence supporting a correspondence of reticular activity with drive level. Belanger and Feldman (reported in Malmo, 1959), Duffy (1932), Freeman (1948), Lindsley (1958, 1961), and Steiner (1962) have shown a direct, though sometimes nonmonotonic, relationship between various physiological measures of arousal level with performance level and/or drive.

Increased attention is presumably a correlate of high drive states, and Galambos (1954, 1956), Granit (1955a, 1955b), Hagbarth and Kerr (1954), Hernandez-Peon et al. (1956), Kerr and Hagbarth (1955), and Rasmussen (1946, 1953) have demonstrated reticular control over sensory input from a number of modalities. In this manner information through one or several sense modalities can be inhibited by means of reticular influences, thus reducing irrelevant noise and allowing focus of attention within one modality.

In addition, high drive states are characterized by increased sensitivity and reactivity to environmental stimuli. Fuster (1958), Fuster and Uyeda (1962), and Isaac (1960) have reduced reaction time with direct

reticular stimulation, and Lindsley (1958, 1961) has shown the same phenomenon with cortical desynchronization. Reticular stimulation has also been shown to increase the resolving power of the cerebral cortex (Lindsley, 1958, 1961) and to lower thresholds for tachistoscopic perception (Fuster, 1958; Fuster and Uyeda, 1962).

A number of studies dealing with humoral and drug effects on the RF and behavior have supported the drive proposition. Bonvallet et al. (1954), Courville et al. (1962) and Dell et al. (1954) have shown that adrenaline stimulates the RF and produces cortical arousal. In addition to the well known role of sympathetic activity in emotional behavior, it has been demonstrated that motivational states of asphyxia (Bonvallet et al., 1954; Dell et al., 1954) and hunger (Holzbauer and Vogt, 1954) increase adrenaline output. Also, Sawyer (reported by Dell, 1958) found that estrus decreased the threshold for cortical arousal with RF stimulation. Bradley (1958) has produced EEG activation with amphetamine and has localized its effect in the reticular formation. A number of behavioral studies have reported a facilitating effect of amphetamine upon performance (Dews, 1958; Morse and Herrnstein, 1956; Skinner and Heron, 1937; Uyeda and Fuster, 1962; and Wentink, 1938), although exceptions exist (Kelleher and Cook, 1959; and Owens, 1960). Chlorpromazine has been shown by Killam and Killam (1958) to depress reticular

arousal, and Posluns (1962) presents data and cites 13 studies demonstrating inhibition of avoidance behavior and activity with chlorpromazine.

Although the above evidence lends impressive support to the drive hypothesis, very few studies have tested the effects of direct reticular stimulation in situations where manipulation of deprivation time or intensity of noxious stimulation have been utilized to establish the concept of generalized drive. In fact, the studies which most closely approach this procedure have reported inhibitory effects of the stimulation. Stimulation of various cerebral structures capable of producing cortical arousal has been shown to inhibit or impair both learning and performance of complicated choice behaviors (Glickman, 1958; Mahut, 1962; Milner, 1954; Proctor et al., 1957; Rosvold and Delgado, 1956; and Thompson, 1958). The areas stimulated in these studies were: medial and intralaminar thalamic nuclei, brain stem RF, posterior hypothalamus, and caudate nucleus. Though these results seem contrary to the drive hypothesis, they may indicate interference with memory rather than drive functions.

In order to study adequately the drive mechanism, rate measures of simple or unlearned responses should be used. In studies of this nature, Chiles (1954) found inhibition of bar pressing for food with medial thalamic

and posterior hypothalamic stimulation, but Mahut (1962) found no effect on running speed or eating behavior with thalamic and brain stem reticular stimulation. Grastyan et al. (1956) applied stimulation to the posterior hypothalamus which facilitated defensive conditioning and inhibited alimentary conditioning. Bloch and Hebb (1956) abolished a simple avoidance response with intralaminar thalamic stimulation, but reticular stimulation had no effect. Sheer (1961) found no effect of posterior hypothalamic stimulation upon a conditioned flexion response, delayed reaction performance, or bar pressing on a VI schedule for food. Ingram (1958) inhibited bar pressing for food with posterior hypothalamic stimulation, but not with caudate stimulation. Finally, to complicate the picture further, Ehrlich (1963) found that tegmental lesions decreased rate of bar pressing for food or water but increased rate of running to obtain food.

In the present study, the midbrain RF was stimulated while animals performed a variety of simple tasks that have been shown to be sensitive to drive effects. Different incentives were sampled in order to test the generality of drive effects that may be produced. Motivational studies that pertain to the tasks used are as follows: (a) Gross locomotor activity is increased under conditions of food deprivation (Hall and Hanford, 1954; Siegel and Steinberg, 1949; and Strong, 1957). (b) Fine activity as seen in the

grooming and scratching behavior of animals is decreased by deprivation (Strong, 1957). (c) The experiments of Alderstein and Fehrer (1955), Dashiell (1925), Fehrer (1956), Thompson (1953), and Zimbardo and Miller (1958) have indicated that high drive increases exploration of a noval environment. (d) Dinsmoor (1952) and Ferster and Skinner (1957) found that increases in deprivation increased the rates of bar pressing on VI and FR schedules respectively. Also, Webb and Goodman (1958) trained animals to press a bar for food, then satiated the Ss and found that covering the floor with water increased the rate of bar pressing. (e) Amsel (1950) and Boren et al. (1959) have demonstrated that increasing the intensity of shock or adding hunger increases the vigor of avoidance behavior.

METHOD

Subjects

Twenty-four male, Long Evans, hooded rats of approximately 70 days of age were obtained from Harland Small Animal Industries. Surgery was performed on all animals of this group, and eight of the rats underwent part or all of the behavioral testing. The experimental subjects were selected primarily on the basis of a lack of forced motor movement from stimulation up to at least 150 uA of current. Other factors such as death and dislodging of electrodes further limited the number of subjects.

Surgery

At about 90 days of age, the subjects received surgical treatment under nembutal anesthesia injected intraperitoneally at a dosage of 60 mg/kg. Each rat was also given 0.2 mg of atropine sulfate intraperitoneally and 60,000 units of penicillin G intramuscularly. The skin on the dorsal surface of the skull was incised and the skull was entered with a #2 trephine. A bipolar electrode of the type described by Valenstein et al. (1961) was lowered stereotaxically into the RF through the trephine opening, according to measurements obtained from

De Groot's coordinates (1959). The coordinates used for the reticular electrodes of the eight experimental animals were 2 mm lateral to the midline, 0.5 mm anterior to the O-O point, and 6 mm in depth from the surface of the cerebral cortex. Variations of 0.5 mm in the anterior-posterior and dorsal-ventral dimensions were introduced in several animals. Reticular electrodes were placed on the right side in 5 experimental Ss and on the left side in 3 animals.

Three stainless steel electrodes, bent at a 90 degree angle 2 mm from one end, were hooked under the skull through small drill holes for supradural electrocorticogram (ECG) recording. The recording electrodes were placed over the frontal, parietal and occipital areas of the side opposite the stimulation electrode. Stainless steel screws were placed in additional drill holes to serve as binding posts for acrylic cement which was used to attach the electrodes to the skull. The skin was closed around the electrodes, leaving an exposed area of acrylic. The wound, however, healed well, and infection was not evident.

Stimulation

Electrical stimulation was delivered to the reticular formation by a Grass model S4E stimulator which was set to provide a train of biphasic pulses of 0.1 msec duration at a rate of 60/sec. The stimulus was fed through an

Argonaut isolation transformer. Current and voltage were monitored on a Tektronix Type 502 dual-beam oscilloscope, and readings were taken from the trailing edge of the distorted square wave. Calculated electrode resistances ranged from about 20,000 to 30,000 ohms.

Electrocorticogram recording

Connections to the cortical recording electrodes were achieved by attaching miniature pin clutches soldered to lead wire. Two Grass Model 5P5 polygraph channels were utilized in obtaining records from frontal-parietal and parietal-occipital leads. The average resistance between electrodes was 20,000 ohms.

ECG testing was first carried out as the animals recovered from surgical Nembutal (pentobarbital sodium). Later, at 250 and 400 days of age, the animals received further testing after injection of 100 mg of Robaxin (methocarbamol). Robaxin presumably acts upon internuncial neurons of the spinal cord, thus facilitating relaxation and drowsiness. Predominantly high amplitude, slow ECG activity is obtained after injection of Robaxin, and arousal from either reticular or natural stimulation occurs more readily with this drug that it does with Nembutal.

Each animal received RF stimulation in an ascending series of 0.5 volt steps, starting at 1.0 volt and ending beyond the ECG activation threshold. This threshold was

defined as the point at which high amplitude, slow activity was completely obliterated by low amplitude, fast activity. After the initial determination of threshold, a number of activation tests were carried out at voltages bracketing the threshold.

Gross observations

On four different occasions, RF stimulation was delivered in an open field for the purpose of observing behavioral signs of arousal. Strength of current was varied in ascending and descending steps of 0.5 volts. The animals' reactions to external stimuli were tested with and without RF stimulation by the following manipulations: (a) The subjects were handled by the experimenter; (b) a pencil was moved before the subjects' faces to test visual following; (c) the animals were lightly prodded and tapped with the pencil; and (d) the experimenter clapped his hands to produce an auditory startle response.

Behavioral tasks

Gross activity (GA):- The animals were placed in an alleyway 24 in. long and 8 in. wide containing photocells that projected across the midpoint of the long sides. A count was obtained each time the rat interrupted the beam, and number of counts was the criterion measure for activity.

Fine activity (FA):- Fine activity was measured in a tilt cage consisting of an 8 in. diameter cylinder

pivoted at the center of its base. Four metal posts, equidistantly placed on the periphery of the base and several mm below the level of the pivotal post, made electrical contact with metal plates affixed to the base. Opposed sets of contacts recorded on the same counter, and an animal's score consisted of the total counts registered on the two counters. This apparatus was extremely sensitive and would count out rapidly for small movements such as those seen with grooming behavior.

Exploration (EX):- The purpose of this task was to determine the number of times subjects would approach a novel object and the amount of time they would spend examining it. Scores for the task were obtained by summing the number of approaches and the time spent sniffing or touching the object. The enclosure used was 24 in. in diameter and contained an "interesting" object that protruded from the center of the floor. The object consisted of a 6 in. high metal spire emerging from concentric cylinders 3/4 in. and 1 1/2 in. in height. Following each two days of testing, another part was added to the spire to maintain novelty. First a spring was attached horizontally from the top, then a yellow wire was hung from the end of the spring, and finally a small bolt and nut were attached to the free end of the wire.

Food reinforcement (FR; FRS):- The animals were trained to obtain 45 mg Noyes lab rat food pellets by

pressing a bar protruding from one wall of a 12 in. square enclosure. Five subjects were trained on a variable interval (VI-30) schedule with a range of five to 55 seconds, and the remaining two animals were trained on a high fixed ration(FR-150) that produced strain. The animals were maintained on an 8-12 hour food deprivation schedule (FR) in order to keep the motivational level low but effective in maintaining stable rates of performance. All subjects were also tested under food satiation (FRS) on an FR-5 schedule.

Sidman avoidance (AV):- The animals were trained to avoid shock to the feet by pressing a bar projecting from one of the short walls of a 12 in. by 6 in. enclosure. The apparatus was dimly illuminated through 1/2 in. holes above the bar and in the top of the enclosure, and through a translucent glass window in the wall opposite the bar. The apparatus was programmed so that electric shock was delivered through a grill if 30 seconds elapsed after a bar press or a previous shock (SS-30-RS-30 schedule). The shock was maintained for a maximum of five seconds and could be escaped by a bar press. Four animals were given a 1000 cps tone and light through the window as warning signals that preceded shock by five seconds and remained on until shock was terminated.

Stimulation valence (VAL):- A test of whether RF stimulation was positively or negatively reinforcing was

given in which the animals could choose between stimulation and no stimulation. A shuttle box was divided by a 2 in. high barrier into two 9 in. by 9 in. compartments with independent brass grill floors. The floors were pivoted at one end and suspended by spring tension at the other so that the weight of an animal tripped a microswitch. The microswitches controlled relays that allowed recording of the time spent in each compartment (the criterion measure) and directed reticular stimulation to the animal only when he was in a particular compartment. The stimulation compartment was changed from day to day.

Behavioral testing procedures

On all tasks except stimulus valence, the subjects daily received ten minutes of testing with stimulation and ten minutes without stimulation. Five minute stimulation (S) and non-stimulation (NS) periods were counterbalanced in the order S-NS-NS-S or NS-S-S-NS. Four consecutive days of testing were given at each stimulation level with the two counterbalanced orders being alternated over days. The stimulation values used for testing were given in the order 10, 25, 50, 75, and 125 uA, with occasional ommission of some levels. For stimulus valence testing, an ascending series was given with two days at each current intensity, followed by a descending series. The intensities of current utilized with each task are indicated in Table 1 of the Results section.

If an animal exhibited consistent facilitatory effects of the stimulation, he received an additional four days of testing at the stimulation intensity and task showing the effect. Consistent facilitation was defined as facilitation occurring on three days out of the four days of testing on one stimulus intensity and task.

Behavioral testing was begun at 120 and continued to 400 days of age. The number of subjects run for all tasks can be found in Table 2. The order of presentation of tasks to the subjects was randomized except that gross activity was the first task and stimulus valence was the last. For food reinforcement and avoidance, the subjects were trained to a stable level of performance before stimulation testing was begun. Training prior to testing was not required with the remaining tasks.

Histology

At the end of the experiment, the brain of each animal, with the electrodes intact, was perfused and fixed in formalin. The electrodes were then removed, and the brains were embedded in celloidin. Serial, coronal sections of 30 micra thickness were cut and appropriate sections were stained with cresyl violet.

RESULTS

ECG activation

Reticular stimulation of all animals proved capable of changing high amplitude, low frequency electrocortical activity to the low, fast, desynchronized pattern typical of activation. Cortical activation thresholds as determined under surgical anesthesia averaged 120 uA. Testing at 250 days of age after injections of Robaxin revealed a lower mean threshold of 40 uA in seven of the animals. The range for these animals was from 25 uA to 60 uA, and threshold for the eighth rat was 260 uA. The thresholds of four animals were obtained at 400 days of age, also under Robaxin, and an average rise intthreshold of 25 uA was observed. The latency of observable activation was typically about one second, and return to high voltage, slow waves usually required approximately two seconds after termination of stimulation. Several animals received stimulation for five minutes and activation was maintained throughout the interval with the usual latency of return to high, slow activity. Samples of reticular induced activation are presented in Fig. 1.

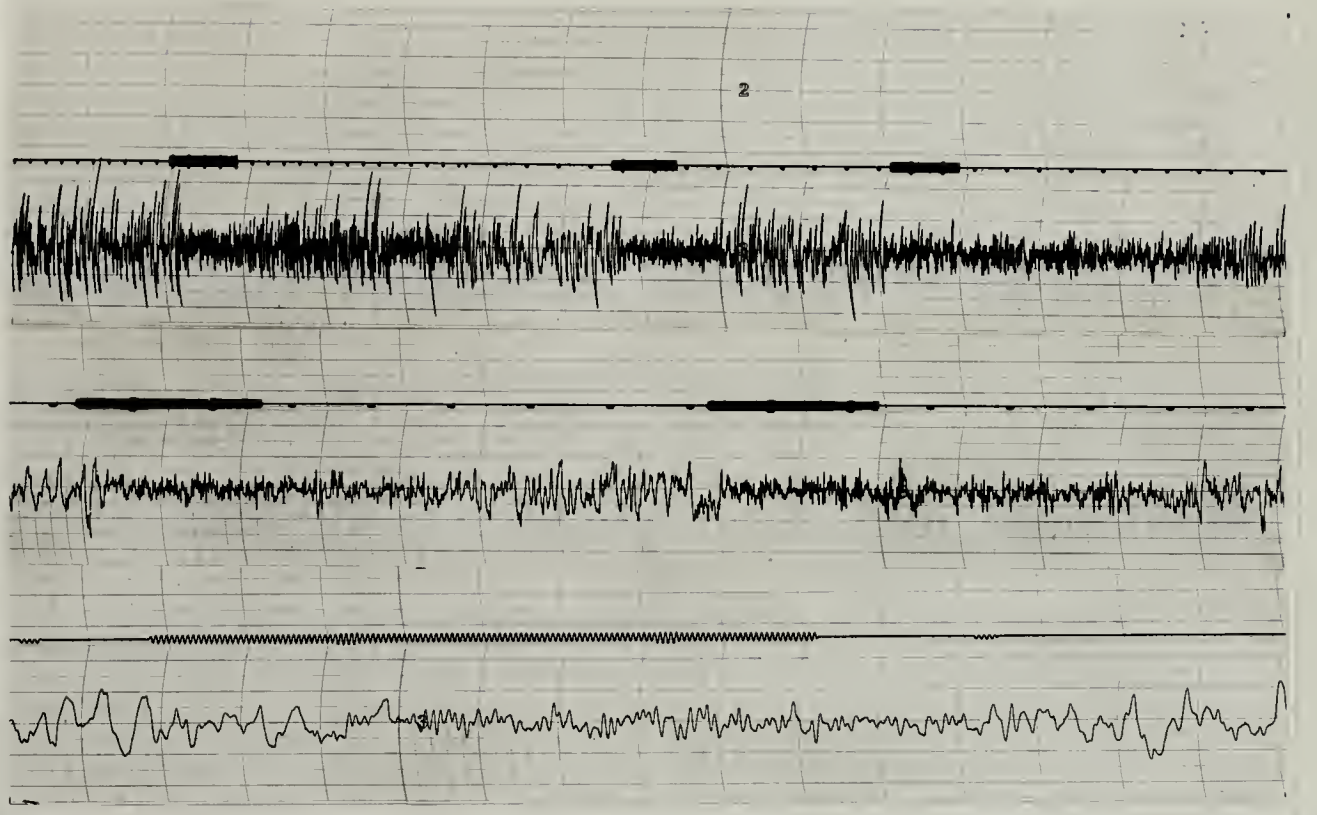

Fig. 1. Electrocorticogram recordings, illustrating arousal induced by reticular stimulation. Time lines appear above the ECG traces to which they refer, with small pips occurring each second and wide bands marking the duration of RF stimulation. The four illustrated paper speeds are 5, 10, 25 and 100 mm/sec, progressing from top left to the bottom trace.

Gross observations

The first grossly observable reaction to RF stimulation typically occurred at a threshold of approximately 50 uA and appeared to be a generalized "alerting". This response involved some or all of the following components: (a) a halting of grooming or perambulation, here referred to as "freezing", (b) forward movements of the pinnae, (c) vigorous movement of the vibrissae and sniffing, (d) exaggerated, irregular respiration, (e) fixation of the head with apparent visual staring, and (f) occasional grinding of the teeth. At 75 uA, external stimuli were presented and produced responses which deviated only slightly from those elicited in the non-stimulation animal. The subjects reacted as usual to handling with no exaggerated struggling. A loud auditory stimulus (hand clapping) produced normal startle responses. Orienting was occasionally seen when a pencil was slowly moved in front of the animals or when it was used to deliver a tap to their backs. More commonly, however, the visual and tactual stimuli were ignored with a relative absence of visual following or turning toward the side tapped.

Within a range of 100 to 250 uA responses were elicited that appeared to be of a "fearful" nature. This involved an increase in muscular tone, freezing into a huddled posture, and occasional bursts of activity in which the animals backed up to a wall or into a corner. Alerting

was pronounced, and the Ss appeared to shrink from an imaginary threat. Several animals would alternately huddle in a corner and vigorously back across the floor to another wall or corner. The animals seemed to ignore visual and tactual stimuli and did not attack or avoid objects placed before them. Auditory startle responses were observed. Upon handling, strong attempts were made to escape the restraint, and biting sometimes occurred.

When the fear response became intense, within a range of 150 to 250 uA, five of the animals leaped spectactularly up the sides of the enclosure. These jumps did not appear to be directly forced by the stimulation. The responses were not stereotyped, coordination was excellent, and the jumps in all cases were well directed toward the top edges of the box. Also, it was discovered that leaps did not occur when the subjects were stimulated while on the laboratory floor, free from restraining walls. In this latter case vigorous running occurred as if designed to escape the vicinity of stimulation.

Forced motor movements were seen between 150 and 250 uA. Six animals exhibited a contralaterally directed concavity of the body and turning of the head. In three of these cases, contralateral circling and/or leaning appeared, but the other three subjects turned ipsilaterally. Thresholds for the responses observed in these animals usually appeared in the order: alerting, fear, forced movement, and jumping.

At threshold current for forced movement, the circling and body concavity could be compensated, and the movements were interrupted by return to normal standing posture. Jumping behavior usually occurred concurrently with forced movement but also appeared in animals not showing the latter.

Behavioral tasks

The predominant effect of reticular stimulation was to inhibit ongoing behavior, as shown by lower scores during stimulation. This effect was consistent among subjects and was significantly present for GA, EX, FA, FR, and AV. As seen in Fig. 2 and Table 1, the amount of inhibition increased from 10 uA through 125 uA, and the majority of significant effects were obtained at the higher intensities. The stimulation also became increasingly noxious as current was increased. Table 1 gives the average difference score (minus signs indicating inhibition and plus signs indicating facilitation) for each task and at all current levels. In Table 2, F-ratios are given in analysis of stimulation effects over all currents, effects between the several stimulation intensities, and the interaction effect between the two treatments.

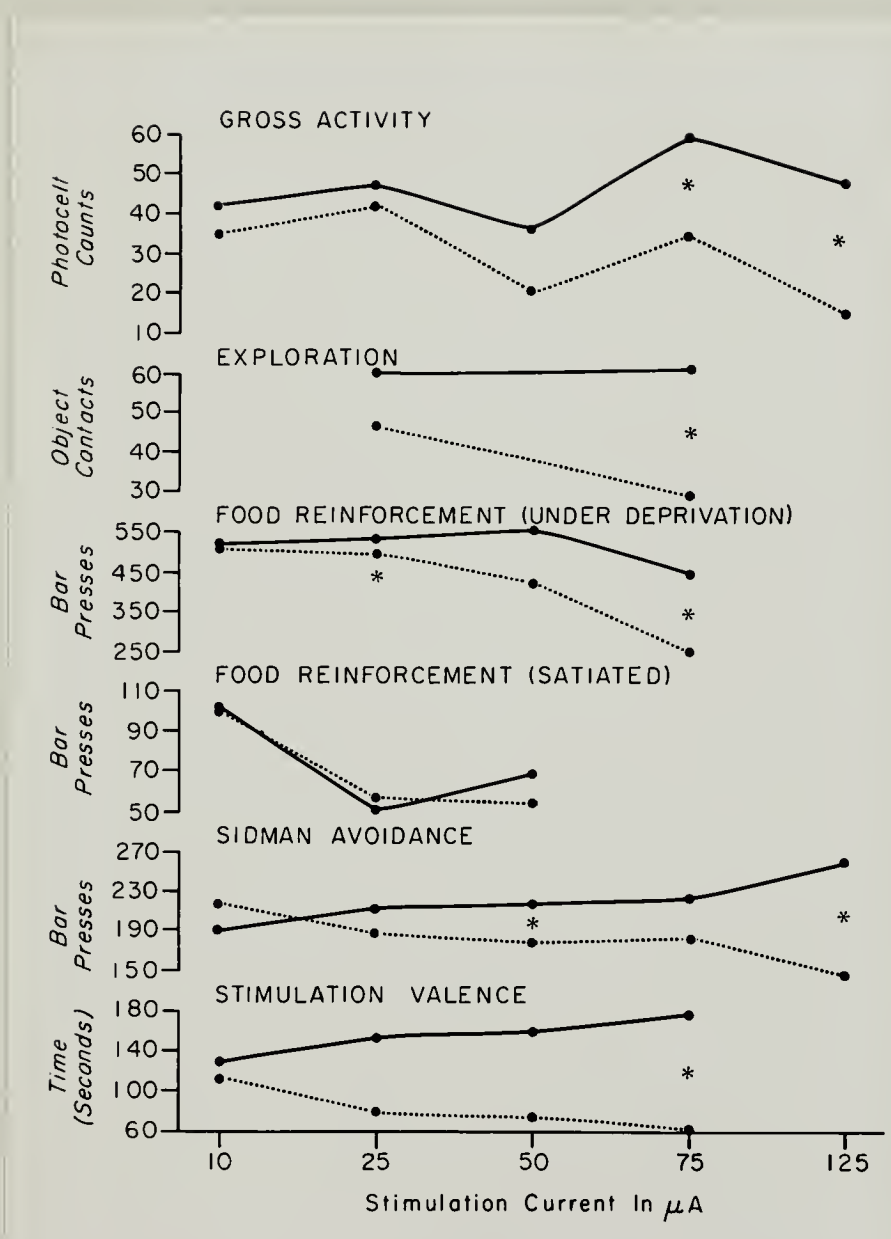

Fig. 2. Behavioral performance without stimulation and as a function of increasing intensity of stimulation. Each point represents an average group score over four days of testing. Stimulation scores are connected by broken lines, and non-stimulation scores are joined by solid lines. Statistical probability of less than 5% as determined by the randomization test for matched pairs (Siegel, 1956) is indicated by the symbol (*).

TABLE 1

Average differences between stimulation (S) and non-stimulation (NS) scores for each task and at each intensity of stimulation. Minus (-) signs indicate greater number of bar presses or activity and exploration counts during the NS periods. Plus (+) signs indicate the opposite. Minus signs for valence of stimulation indicate more time spent without stimulation. Abbreviations are as follows: GA - gross activity, EX - exploration, FA - fine activity, FR - food reinforcement, FRS - satiated food reinforcement, AV - Sidman avoidance, VAL - valence of stimulation, and D - average difference scores.

		10 uA	25 uA	50 uA	75 uA	125 uA
GA	D	- 7.4	- 5.9	- 15.2	- 24.7*	- 33.3*
EX	D		- 13.3		- 32.3*	
FA	D		-328.31*			
FR	D	- 13.4	- 37.4*	-127.3	-201.9*	
FRS	D	- 1.4	+ 4.2	- 14.2		
AV	D	+ 10.7	- 24.0	- 37.9*	- 39.3	-113.4*
VAL	D	- 15.3	- 63.7	- 75.8	-114.9*	

* indicates statistical probability of less than 5% as determined by the randomization test for matched pairs (Siegel, 1956).

TABLE 2

Treatment (S vs. NS) by treatment (uA) by subjects analysis of variance,[a] showing F-ratios for the two main effects and the interactions between these effects. The abbreviations are as in Table 1.

	N	S-NS (df)	uA (df)	S-NS x uA (df)
GA	8	5.53 (1/7)	0.65 (4/28)	2.17 (4/28)
EX	7	5.50 (1/6)	2.54 (1/6)	2.30 (1/6)
FR	7	6.75* (1/6)	2.41 (3/18)	2.34 (3/18)
FRS	5	0.05 (1/4)	1.60 (2/8)	0.30 (2/8)
AV	7	6.04* (1/6)	0.04 (4/24)	3.80*(4/24)

[a] The statistical analysis was taken from Lindquist (1953).
* indicates statistical probability of less than 5%.

Undoubtedly, the attainment of statistical significance of reticular inhibition has been made difficult by several features of the experimental design. For example, the variability of scores was increased for the food reinforcement and Sidman avoidance tasks by changing the conditions for some of the animals. This was done in an attempt to find a procedure that might be sensitive to facilitatory effects of stimulation. Also, the variability of scores was probably increased by testing the animals, in most cases, under low levels of drive. Weak current levels were chosen with the expectation that facilitation would occur at these levels if at all. Preliminary testing with several animals at current values just below threshold

for jumping and forced movement indicated that these values produced dramatic inhibition of performance. In view of these factors, a nonparametric, randomization test was used for the analysis of differences between S and NS scores at each current level of each task.

As seen in Table 2, significant inhibition of bar pressing over all current intensities was found for avoidance and food reinforcement. In addition, the significant interaction for avoidance was produced by an increasing number of NS bar presses from 10 to 125 uA and a decreasing number of S presses. This same trend was observed with all other tasks except FRS.

Retests of animals showing consistent facilitation over four days at a particular current level and task did not reproduce the facilitation in any case. The average of six retest scores was -28.2. No one animal or task was repeatedly represented in the reruns. All but one instance of original facilitation occurred at 10 or 25 uA. One animal that was tested for 16 days on FR at 10 uA exhibited a consistent and significant facilitatory effect of stimulation. This animal did not show the facilitation in any other situation and, in fact, was markedly inhibited by the stimulation in many cases.

In general, valence of stimulation scores revealed an increasing aversiveness of the stimulation from 10 to 75 uA. Only one animal preferred the stimulation, and this

effect was prominant only at 25 uA, changing to aversiveness at 50 and 75 uA. The only consistant effect observed for this animal at 25 uA was inhibition of exploration. Two animals revealed no marked seeking or avoidance of the stimulation at any current level but distributed their choices randomly. Both these animals were considerably inhibited by stimulation on several tasks, primarily at 75 uA and above, but on one occasion at 25 uA.

Histology

The reticular electrode placements, as verified histologically, are diagrammatically presented in Fig. 3. The range of placements was 5 to 6 1/2 mm ventral to the cortex, 1.5 to 2.5 mm lateral to the midline, and 0.5 to 1.5 mm anterior to the 0-0 point. The placements were closely grouped, and all were within the dorsolateral reticular substance.

Fig. 3. Diagrammatical representation of electrode tip placements in the dorsolateral midbrain reticular formation. Dorsal-ventral and lateral dimensions are indicated in mm. The drawing is taken from De Groot (1959, p. 37), and the level of section is 0.5 mm anterior to the 0-0 point. Distances anterior to the 0-0 point are indicated by solid circles (0.5 mm), open circles (1.0 mm), and a square (1.5 mm).

DISCUSSION

The grossly observable alerting effect has been noted by a number of investigators and appears to be an invariant response to reticular stimulation of moderate to high intensity. It is interesting though, that the alerted animals in this study were less responsive to external stimuli. This was seen as a diminution in visual following, orienting to a tactual stimulus, and exploration of a novel stimulus. The alerting may be comparable to the arrest reaction produced by Hunter and Jasper (1949) to intralaminar and medial thalamic stimulation. The thalamic reaction seems to be more extreme, however, since Hunter and Jasper saw no auditory startle response or visual following.

The forced contralateral head turning and body concavity is contrary to the ipsiversive tegmental response that has frequently been reported (see review by Skultety, 1962). Turning or circling was variable in the present study and does not remove the discrepancy. However, Skultety (1962) found contralateral turning with dorsolateral midbrain placements in the cat that correspond roughly with those of the present study. Based on his work and that of Sprague and Chambers (1954) with lower brain stem placements,

Skultety proposed a medial (ipsiversive)-lateral (contraversive) division that is supported in part by the present study.

Behaviors very similar to the fear reaction of this study have been evoked by a number of investigators from diencephalic and midbrain structures (Delgado, 1955; Delgado et al., 1954, 1956; Fernandez De Molina and Hunsperger, 1959, 1962; Masserman, 1941; Roberts, 1958, 1962; Segundo et al., 1955; and Spiegel et al., 1954). Roberts and Delgado et al. have shown that animals can learn to avoid stimulation of "alarm" points in the dorsomedial and lateral thalamus, the tectal area, the medial lemniscus, and the inferomedial hippocampus, though avoidance learning was not obtained from "flight" points in the posterior hypothalamus. If tegmental stimulation produces a true fear reaction, as these studies suggest, then it would seem that avoidance performance should have been facilitated in the present study.

The inhibition of reticular stimulation upon performance was consistent, with the exception of one animal showing facilitation on the VI-30 schedule at 10 uA. Valence of stimulation was not determined for that animal because of early death, and neither his electrode placement nor behavior on other tasks give a clue to the reason for this isolated finding. Reticular stimulation became increasingly noxious and increasingly inhibitory as current

was increased, but a causal relationship should not be assumed. Two animals demonstrated behavioral inhibition with no evidence of escaping the stimulation. It is also interesting to note that significant inhibition occurred with fine activity and food reinforcement at 25 uA, which was below the average ECG arousal threshold. This is not particularly surprising, however, since that stimulation was delivered to an awake, aroused animal.

It is improbable that reticular induced inhibition is specific to certain parameters of the electrical stimulus. A wide range of current intensities was sampled in the experiment proper, and frequencies from 1 to 300/sec were used in preliminary testing on gross activity. Facilitatory effects were not observed throughout the frequency range. In most cases, tegmental stimulation did not abolish activity, exploration, or operant behavior but decreased rate to a degree related to the intensity of stimulation. That is, the correspondence of amount of inhibition with current value was not the result of averaging data of an all-or-none nature.

Studies showing facilitation of performance with drug intervention or spontaneous, generalized activation are not conclusive evidence of reticular mediated drive, since the cerebral structures involved in the initiation of this arousal are not definite. The studies of Lindsley, Fuster and Isaac, demonstrating enhancement of reaction time,

perception, and cortical receptivity with direct RF stimulation, are more difficult to reconcile with the present study. Unless species differences are a crucial factor, it appears that reticular stimulation facilitates perceptual processes and inhibits performance, and reasons for this apparent contradiction must be sought.

It is probable that stimulation in the reticular substance near the medial lemniscus and colliculi produces sensory effects including pain. In fact, Spiegel and Wycis (1961) have stimulated the reticular formation of humans subsequent to midbrain spinothalamic lesions, and elicited reports of pain which was projected to the opposite side. Such pain could elicit the fear reaction, and either or both factors would serve as distracting influences to a performing animal. Even in an avoidance situation, bar pressing to avoid shock might extinguish during stimulation periods, since relief from centrally elicited pain and fear is not achieved. It would seem that such distracting influences should have also impaired performance in Fuster's study of tachistoscopic perception, but the nature of the task and the response required may play an important role. Fuster's animals were well trained, and the response was a discrete occurrence following upon observance of only one of the briefly illuminated objects. Possibly a distracting stimulus must be intense to inhibit this reaction as compared to repetitive, sequential, or complex responses,

which may be disrupted by relatively mild stimulation. Also, the arrest of activity and alerted posture resulting from RF stimulation might conceivably enhance perception but antagonize maintenance of a steady rate of responding.

Another source of explanation is offered by the inverted U hypothesis of arousal proposed by Malmo (1958). He has reviewed evidence indicating that intense activation impairs performance on tasks measuring rate of performance and vigilance. Two factors may be of importance here: (a) The effect has not been demonstrated with tasks involving discrete trials widely spaced in time, and (b) it may be difficult to produce subtle increases in activation with electrical stimulation. The latter point, however, was not supported by the ECG activation records obtained in this study. ECG arousal did not appear to be an all-or-none phenomenon, but as stimulating current approached threshold, amount of low voltage, fast activity increased until high voltage, slow activity was obliterated.

Several other possibilities should be considered for future research. It is conceivable that direct chemical stimulation of the RF would more closely simulate natural arousal than electrical stimulation. According to Rinaldi and Himwich (1955), and Steiner and Himwich (1962), arousal can be obtained with adrenergic stimulation in the pontine reticular formation, and cholinergic stimulation in the mesodiencephalic activating system.

Also, in view of recent evidence suggesting anatomical and functional differentiation within the brain stem RF (Batini et al., 1959a, 1959b; Batsel, 1960; Bonvallet and Bloch, 1961; Brodal, 1957; Feldman and Waller, 1962; Huttenlocher, 1961; Jouvet, 1961; and Schlag et al., 1962), a more detailed exploration of specific reticular areas with electrical stimulation may be of value. In this regard, it should be noted that Fuster found facilitatory effects with dorsal midbrain placements comparable to those of the present study. Nevertheless, there remains the possibility that separate reticular areas differentially express perceptual and motivational functions.

SUMMARY

Eight animals were stimulated within the dorsolateral midbrain reticular formation while performing in situations designed to be sensitive to variations in drive level. Amount of gross activity, fine activity, exploration, and bar pressing to obtain food and avoid shock was suppressed as an increasing function of stimulating current from 10 to 125 uA.

Electrocortical activation was seen in all animals with reticular stimulation, and grossly observable alerting, fear, and forced motor reactions were described. The reward value of stimulation was tested in the majority of animals, and an increased tendency toward escape of the central stimulus was seen with increasing amperage.

It was concluded that direct midbrain reticular excitation does not produce the expected increase in motivational level that would be evidenced as facilitation of a wide variety of activities.

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APPENDIX

Raw Data. Each score for GA, FA, EX, FR, FRS and AV is the sum of measurements obtained over 4 days (40 minutes). VAL scores are in minutes, 240 minutes being the maximum value possible.

Task	Animal	Non-stimulation (NS) uA 10	25	50	75	125	Stimulation (S) uA 10	25	50	75	125
GA	15	0	11	31	57	52	14	13	0	20	6
	16	34	41	48	94	1888	38	16	20	9	67
	17	62	9	13	0	12	70	12	0	0	4
	18	42	34	31	43	42	17	49	48	49	20
	19	0	9	3	3	2	1	2	0	1	11
	20	47	27	11	10	24	25	19	17	20	7
	21	105	170	115	175	57	81	131	47	118	5
	23	45	80	33	94	9	30	92	31	61	0
retest	15	(23)					(1)				
retest	23		(42)					(46)			
FA	15		1016					533			
	16		1547					943			
	17		585					559			
	18		434					432			
	19		748					73			
	21		1932					1467			
	23		2027					1984			

Raw Data. Continued

Task	Animal	Non-stimulation (NS) uA 10	25	50	75	125	Stimulation (S) uA 10	25	50	75	125
EX	15		5		0			5		3	
	17		107		108			52		43	
	18		36		36			47		35	
	19		34		61			25		2	
	20		15		0			14		0	
	21		121		118			65		76	
	23		104		105			122		44	
retest	23		(108)					(27)			
FR	16	403	467	488	578		436	407	224	30	
	17	429	526	437	264		291	547	499	95	
	18	994	988	977	663		995	925	621	99	
	19	354	308	321	167		326	270	346	241	
	20	676	839	943	648		731	808	903	548	
	21	254	270	446	475		314	249	112	371	
	23	588	343	299	404		511	273	315	402	
retest	17			(495)					(392)		
retest	21	(307)					(267)				

Raw Data. Continued

Task	Animal	Non-stimulation (NS) uA 10	25	50	75	125	Stimulation (S) uA 10	25	50	75	125
FRS	17	168	36	64			170	39	63		
	18	60	17	58			58	34	26		
	19	19	56	96			25	106	57		
	20	212	52	89			231	43	136		
	23	84	98	51			60	58	29		
AV	15	205	300	217	236	298	216	167	133	181	128
	17	231	207	209	234	448	230	241	190	150	159
	18	140	114	192	162	219	229	104	174	170	188
	19	181	120	146	162	135	152	114	128	156	112
	20	186	168	196	175	160	174	156	143	170	172
	21	289	496	428	457	438	400	445	362	325	159
	23	107	80	123	135	114	113	90	116	134	100
retest	18	(146)					(159)				
VAL	17	116	30	147	229		126	211	95	11	
	18	180	223	164	197		70	17	82	43	
	19	129	162	179	175		113	79	71	65	
	20	102	145	120	125		144	96	119	114	
	21	124	166	227	220		117	72	13	20	
	23	124	185	121	118		124	55	124	122	

Raw Data.

Animal	Threshold in uA						Electrode Placement	Body Movement Direction	Circling Direction
	EEG (Nembutal)	EEG (Robaxin, 250 days of age)	EEG (Robaxin, 400 days of age)	FEAR	FORCED MOVEMENT	JUMPING			
15	140	40		175	175	----	L	R	R
16	120	60		100	150	150	R	----	R
17	150	45	80	100	----	175	L	----	----
18	115	35		125	150	250	R	L	R
19	100	45	70	200	200	250	R	L	R
20	110	260	160	150	200	----	L	R	R
21	110	25		100	150	175	R	L	L
23	150	45	180	150	150	----	R	L	R

VITA

Charles John Vierck, Jr. was born July 6, 1936 in Columbus, Ohio, and attended public school there until graduation from Upper Arlington High School in 1954. As an undergraduate the author attended Ohio State University and the University of Florida. In January, 1959, he received the B.S. degree from the University of Florida with a group major in biology, chemistry, and psychology. The M.S. and Ph.D. degrees were also taken at the University of Florida in June, 1961, and August, 1963. His area of specialization is physiological psychology.

The author served as Research Assistant at the University of Florida from 1959 to 1961 and at Vanderbilt University in the summer of 1961. In 1961-1963, he was supported by the National Institute of Mental Health as a Research Fellow. The author is married to the former Norma Lee Higginson of Jacksonville, Florida.

This dissertation was prepared under the direction of the chairman of the canditate's supervisory committee and has been approved by all members of that committee. It was submitted to the Dean of the College of Arts and Sciences and to the Graduate Council, and was approved as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August 10, 1963.

Dean, College of Arts and Sciences

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